IFW AF/1647

Application No. 09/826,463
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the Application of

Nobuto YAMAMOTO

Application No.: 09/826,463

Filed: April 5, 2001

Group Art Unit: 1647

Examiner: David S. Romeo

Docket No.: Y1004/20017

For: PREPARATION OF POTENT MACROPHAGE ACTIVATING FACTORS DERIVED FROM CLONED VITAMIN D BINDING PROTEIN AND ITS DOMAIN AND THEIR THERAPEUTIC USAGE FOR CANCER, HIV-INFECTION AND OSTEOPETROSIS

BRIEF ON APPEAL

Appeal from Group 1647
Caesar, Rivise, Bernstein
Cohen & Pokotilow, Ltd.
12th Floor, 7 Penn Center
1635 Market Street
Philadelphia, PA 19103-2212
(215) 567-2010
Attorneys for Appellant

TABLE OF CONTENTS

I. INTRODUCTION

A. Real Party in Interest

The real party in interest for this Appeal and the present application is the sole inventor, Nobuto Yamamoto.

B. Statement of Related Appeals and Interferences

There are presently no appeals or interferences, known to appellant or appellant's representatives (there is no assignee), that would directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

C. Status of Claims

Claim 22 is pending. Claim 22 stands finally rejected and is on appeal. The appealed claim is set forth in the Appendix.

D. Status of Amendments

There are no Amendments pending.

II. SUMMARY OF INVENTION

Inflammation results in the activation of macrophages. See the instant specification at page 4. This macrophage activation requires participation of B and T lymphocytes and serum vitamin D binding protein (DBP; human DBP is known as Gc protein). *Id.* *In vitro* activation of macrophages by lyso-PC requires the step-wise modification of Gc protein by β-galactosidase of lyso-Pc-treated B cells and sialidase of T cells to generate the macrophage activating factor (MAF), a protein with N-acetylgalactosamine as the remaining sugar moiety. *Id.* Thus, Gc protein is a precursor for MAF. Specification at page 5.

Incubation of Gc protein with immobilized β-galactosidase and sialidase generates remarkably high titered MAF (GcMAF). *Id.* Administration of a minute amount of GcMAF has greatly enhanced phagocytic and superoxide generating capacities of macrophages. *Id.*

Loss of the MAF precursor activity prevents generation of MAF. *Id.* Lost or reduced precursor activity of Gc protein was found to be due to deglycosylation of plasma Gc protein by α-N-acetylgalactosaminidase detected in cancer and HIV patients. *Id.* Deglycosylated Gc protein cannot be converted to MAF. *Id.* Thus, plasma α-N-acetylgalactosaminidase appears to play a role in immunosuppression in cancer and HIV patients. However, exogenously given MAP (or GcMAF) bypasses inactive (deglycosylated) Gc protein and acts directly to activate macrophages to eradicate disease (e.g., cancer, HIV).

Claim 22 on appeal is directed to a method for producing a cloned macrophage activating factor (GcMAFc), comprising cloning a Gc1 isoform into a baculovirus vector, **expressing** the cloned Gc1 isoform, contacting the cloned Gc1 isoform with immobilized β-galactosidase and sialidase, and obtaining the GcMAFc.

III. ISSUES

A. Whether the Examiner has failed to show that claim 22 is obvious under 35 U.S.C. § 103(a) as being unpatentable over Yamamoto (A) in view of Cooke (U), Quirk (U), Lichenstein (A), Murphy (B), and Luckow (V).

IV. GROUPING OF CLAIMS

There is only one claim on appeal.

V. ARGUMENT

A. Whether the Examiner has failed to show that claim 22 is obvious under 35 U.S.C. § 103(a) as being unpatentable over Yamamoto (A) in view of Cooke (U), Quirk (U), Lichenstein (A), Murphy (B), and Luckow (V).

In the Final Office Action the Examiner rejects claim 22 solely over "Yamamoto (A) in view of Cooke (U), Quirk (U), Lichenstein (A), Murphy (B), and Luckow (V)." See Final Rejection at page 2, lines 21-26. However, the Examiner still fails to show that claim 22 is obvious for the reasons discussed below.

The burden is on the Patent Office to make an initial showing of *prima facie* obviousness to support a rejection under 35 U.S.C. § 103. M.P.E.P. § 2142. According to M.P.E.P. § 2143, the three basic elements of a *prima facie* showing are: (i) there must be a suggestion or motivation to modify the applied reference and/or combine reference teachings; (ii) there must be a reasonable expectation of success in making the modification and/or combination; and (iii) the modified and/or combined teachings must teach or suggest all the claim limitations. The Office has failed to make such a showing.

(i) The proposed combination of teachings

The Final Rejection purports to show the obviousness of the pending claims by combining (1) the process of converting glycosylated Gc protein (Gc isoform) to a highly potent macrophage activating factor (GcMAF), as taught by Yamamoto; (2) the amino acid sequence of the Gc protein, and the nucleotide sequence encoding the protein, as taught by Cooke et al.; (3) the production of recombinant proteins, as taught by Quirk et al.; (4) the cloning of a novel protein, known as afamin (AFM), which belongs to the group of human serum proteins including

vitamin D binding protein, as taught by Lichenstein[1]; (5) baculovirus vectors to express glycosylated recombinant proteins late in infection, as taught by Murphy; and (6) the process for expressing exogenous proteins in insect cells using baculovirus expression vectors, as taught by Luckow.

(ii) No motivation to modify with a reasonable expectation of success

An ordinarily skilled artisan would not have had a reasonable expectation of successfully reaching the claimed invention based upon the teachings in the references cited by the examiner. To begin with, Yamamoto does not teach the cloning of the Gc protein into a baculovirus vector and Luckow teaches only generic applications regarding the use of baculoviruses as vectors. Moreover, the Office Action does not show how or where Luckow teaches that a baculovirus vector could be successfully employed to express the GcMAF protein in all insect cells. The mere fact that Luckow describes several successful examples comprising the use of a baculovirus vector to express certain proteins in insect cells, without any showing by the Office that such proteins are substantially analogous to, and reasonably predictive of, GcMAF, does not sustain the Office's burden of showing that an ordinarily skilled artisan would have been motivated to have made the proposed combination of reference teachings, and would have had a reasonable expectation of success in doing so. See, e.g., *In re Vaeck*, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991).

In fact, none of the cited references show how to clone the GcMAF or a substantially analogous protein into a baculovirus vector. Cooke discloses both the nucleotide and amino acid sequences of the vitamin D binding protein although all of the cloning was performed with

[1] Structurally, Gc protein is o-glycosylated, while all other serum proteins are not. Thus, the afamin protein is not analogous to Gc protein).

standard plasmid vectors in bacteria. Lichenstein discloses the cloning of a novel member of the human serum albumin protein family; however, it provides no guidance on how to clone the GcMAF protein of the present invention. The Gc protein is a soluble membrane protein unlike the albumin protein which is a serum protein. Also, Lichenstein neither mentions nor teaches the use of baculovirus vectors for cloning and expression purposes. The Examiner referred to Lichenstein as stating that "host cells from mammals, prokaryotes, fungi, yeast, insects and the like are used for the recombinant expression of AFM." (column 13, lines 52-55). However, merely stating that something is possible does not render it so. This statement was made as a general comment in the background section of this patent and there is no evidence in Lichenstein to support it. The only type of cloning that is performed in Lichenstein is with the use of a bacterial expression vector, not a baculovirus vector. Also, Quirk teaches how to express and purify human serum albumin in brewer's yeast. As such, it provides no teaching of how to clone GcMAF or any members of the human serum protein albumin (ALB) family with the use of a baculovirus vector. All members of the albumin family are not o-glycosylated. Even serum proteins are not o-glycosylated and thus Gc protein is unique.

The Examiner also cites Murphy as providing vectors to express recombinant proteins during baculovirus infection. Specifically, Murphy discloses several baculovirus vectors that are useful in generating glycosylated proteins in the late term of infection. As the Examiner pointed out in the Final Rejection (page 5, lines 10-11), Murphy states that these vectors may be useful for the expression of a wide variety of proteins, including blood proteins. However, the only protein that Murphy expressed with this method is the gp120 HIV glycoprotein. Unlike the Gc protein, gp120 is not sialylated and there is no evidence in Murphy to suggest that a sialylated protein could be generated as easily in insect cells. Also, there are some baculovirus infected

insect cells that do not produce sialylated proteins efficiently unless they are genetically engineered to do so (i.e., transfection with sialyltransferase or a sialic acid synthetase). In fact, Luckow at pages 15-16 acknowledges the unpredictability of foreign glycosylated protein expression by baculovirus vectors:

> Differences in the microheterogeneity of oligosaccharide structures are often observed for mammalian glycoproteins expressed in different mammalian cell lines or by individual cell lines under different culture conditions, which may or may not reflect the structure or heterogeneity of the protein in its "native" environment.

Taken together, these references hardly provide the type of teaching that would cultivate confidence in a skilled artisan, and serve as the basis for a reasonable expectation of success in cloning the Gc protein in a baculovirus vector.

The present facts are sufficiently similar to those of *Vaeck* to warrant a discussion of the case, and how the Federal Circuit's holding in that case should guide the Board's decision in this appeal. In *Vaeck*, the Federal Circuit reversed the obviousness rejection of claims to a chimeric gene capable of being expressed in Cyanobacteria cells, comprising (1) a nucleotide promoter region effective for expression in Cyanobacteria, and (2) a nucleotide fragment coding for an insecticidally active protein. *Vaeck* at 1439-40. The Office had rejected the claims as being obvious over prior art that taught the expression in Cyanobacteria of a chimeric gene comprising (1) a nucleotide promoter region effective for expression in Cyanobacteria, and (2) a nucleotide fragment coding for chloramphenicol acetyl transferase (CAT), an antibiotic resistance-conferring gene used as a marker. *Id.* The court found that the Office had not established the *prima facie* obviousness of the claimed subject matter because:

> The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in [the primary reference] of

> substituting in the disclosed plasmid a structural gene encoding Bacillus insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

Vaeck at 1443.

Thus, here as in *Vaeck*, there is no showing of *prima facie* obviousness because there is no showing by the Examiner that the applied art suggests a reasonable likelihood of success in substituting the structural gene encoding Gc protein for the structural genes which Luckow discloses have been successfully incorporated into baculovirus vectors. Luckow and Murphy are integral to the Examiner's rejection, as they are the only cited references that disclose the use of a baculovirus vector for cloning. The Examiner bases his purported *prima facie* case on the proposition that Luckow teaches that the baculovirus vector is a universally effective expression vector for all structural genes. However, as stated above, this is not what Luckow teaches.

As in *Vaeck*, it is incumbent upon the Examiner to show that Luckow discloses the successful expression of a gene sufficiently similar to the Gc protein-encoding gene that one of ordinary skill in the art would have had a reasonable expectation of successfully expressing Gc protein in a baculovirus vector.

(iii) Further significance of claim 22 over the applied art

The peptide sequence of GcMAF is the peptide sequence of native plasma Gc protein, as opposed to a mutant form of GcMAF. Thus, the peptide of GcMAFc should be the same peptide of native plasma Gc protein before treatment with immobilized β-galactosidase and sialidase. Protein synthesis in the cloning apparatus occasionally yields mutant Gc peptides having an amino acid substitution due to mistakes made during gene copying processes. However, most of

these mutant Gc peptides become functional GcMAFc obtained after treatment of these mutant peptides with immobilized β-galactosidase and sialidase and, therefore, are likely to be immunogenic (anaphylactic) in humans. Thus, only the cloned Gc protein having the wild type peptide sequence is to be used to generate the cloned GcMAFc of this invention. None of the references cited by the Examiner make this distinction.

VI. CONCLUSION

The applied references do not properly combine to anticipate or render obvious the claimed invention. Accordingly, the Honorable Board of Patent Appeals and Interferences is respectfully requested to the claim rejection and pass this application on to issuance.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

June 11, 2004

By_____

Robert S. Silver
Registration No. 35,681
Seven Penn Center
12th Floor
1635 Market Street
Philadelphia, PA 19103-2212
(215) 567-2010
Attorneys for Applicant

Attachments:
In re Vaeck
Appendix

APPENDIX: APPEALED CLAIM

A process for producing a cloned macrophage activating factor (GcMAFc) comprising:

(a) cloning a Gc1 isoform into a baculovirus vector;

(b) expressing the cloned Gc1 isoform, thereby producing a cloned Gc1 protein, wherein the Gc1 protein comprises approximately 458 amino acids with a molecular weight of approximately 52,000 Da and 3 distinct domains;

(c) contacting the clones Gc1 protein a molecular weight of approximately 52,000, approximately 458 amino acids and 3 distinct domains in vitro with immobilized bets galactosidase and sialidase, and

(d) obtaining the cloned macrophage activating factor (GcMAFc).

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 165.00

Complete if Known	
Application Number	09/826,463
Filing Date	April 5, 2001
First Named Inventor	Nobuto Yamamoto
Examiner Name	David S. Romeo
Art Unit	1647
Attorney Docket No.	Y1004/20017

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 03-0075

Deposit Account Name: Caesar, Rivise et al.

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) -0-

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X	=	
Independent Claims		- 3** =		X	=	
Multiple Dependent					=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) -0-

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	165.00
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
				Other fee (specify)	

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 165.00

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Robert S. Silver	*Registration No. (Attorney/Agent)*	35,681	*Telephone*	215-567-2010
Signature				*Date*	June 11, 2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

SUBSTITUTE PTO/SB/21 (02-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/826,463
Filing Date	April 5, 2001
First Named Inventor	Nobuto Yamamoto
Art Unit	1647
Examiner Name	David S. Romeo
Attorney Docket Number	Y1004/20017

Total Number of Pages in This Submission: 13

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form (In duplicate)
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment and Cover Sheet
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Technology Center (TC)
- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Return Receipt Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Robert S. Silver Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
Signature	
Date	June 11, 2004

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Robert S. Silver		
Signature		Date	June 11, 2004